American Journal of Medical Genetics (Neuropsychiatric Genetics) 105:369–374 (2001)

Scanning of Estrogen Receptor α (ERα) and Thyroid Hormone Receptor α (TRα) Genes in Patients With Psychiatric Diseases: Four Missense Mutations Identified in ERα Gene

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Estrogen and thyroid hormones exert effects on growth, development, and differentiation of the nervous system. Hormone administration can lead to changes in behavior, suggesting that genetic variants of the estrogen receptor α (ERα) and the thyroid hormone receptor α (TRα) genes may predispose to psychiatric diseases. To investigate this possibility, regions of likely functional significance (all coding exons and flanking splice junctions) of the ERα and TRα genes were scanned in patients with schizophrenia (113), along with pilot studies in patients with bipolar illness (BPI), puerperal psychosis, autism, attention-deficit hyperactivity disorder (ADHD), and alcoholism. A total of 1.18 megabases of the ERα gene and 1.16 megabases of the TRα gene were scanned with Detection of Virtually All Mutations-SSCP (DOVAM-S), a method that detects virtually all mutations. Four missense mutations, seven silent mutations and one deletion were identified in the ERα gene, while only four silent mutations were present in the TRα gene. Two of the missense mutations in ERα are conserved in the six available mammalian and bird species (H6Y, K299R) and a third sequence variant (P146Q) is conserved in mammals, birds, and *Xenopus laevis*, hinting that these sequence changes will be of functional significance. These changes were found in one patient each with BPI, puerperal psychosis, and alcoholism, respectively. Analysis of the ERα and TRα genes in 240 subjects reveals that missense changes and splice site variants are uncommon (1.7% and 0%, respectively). Further analyses are necessary to determine if the missense mutations identified in this study are associated with predisposition or outcome for either psychiatric or nonpsychiatric diseases.

KEY WORDS: ERα; TRα; schizophrenia; psychiatric diseases; DOVAM-S; mutation detection

INTRODUCTION

Estrogen receptor (ER) is a nuclear protein and a member of the steroid/nuclear receptor superfamily (e.g., glucocorticoid receptor and thyroid hormone receptor) that share a highly conserved structure and a common mechanism affecting gene transcription. Two forms of the ER are now known: ERα and ERβ. ERα is generally the most abundant. ERα gene is cloned and localized on chromosome 6q25.1 [Green et al., 1986; Menasce et al., 1993]. ERα receptor messenger RNA is expressed in discrete areas of the human brain related

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Received 21 August 2000; Accepted 1 March 2001
Published online 30 April 2001

not only to neuroendocrine function, but also emotion, memory, and cognition [Osterlund et al., 2000]. This is consistent with the hypothesized involvement of estrogen in schizophrenia and/or affective disorders. Moreover, the estrogen receptor α gene was also reported as a positional candidate gene for schizophrenia [Cao et al., 1997; Levinson et al., 2000].

Female hormones, estrogen in particular, may play an important role in neuropsychiatric disorders. Women experience the onset of schizophrenia at a significantly later age than men and seem to respond better to antipsychotic drug treatment when they are young [Seeman, 1996, 1997]. One hypothesis is that estrogen may ameliorate the symptoms of schizophrenia, and estrogen treatment has shown some beneficial effects in patients with schizophrenia [Hafner et al., 1993]. While the incidence of bipolar illness (BPI) is equivalent in men and women, the course of the illness tends to differ by gender [Leibenluft, 1996]. Bipolar women are more likely than bipolar men to develop the rapid-cycling form of the illness. The time of greatest risk of developing a manic episode for women with a predisposition to bipolar disorder is during the first 2 weeks after childbirth [Dean and Kendell, 1981]. Postpartum mania occurs in the context of a rapid and dramatic decrease in circulating estrogen levels after delivery [Silverstone and Romans-Clarkson, 1989].

Thyroid hormones regulate growth, development, and differentiation, and their actions are mediated by the thyroid hormone receptors (TRs). Considerable attention has been directed toward the hypothalamic-pituitary-thyroid (HPT) axis and its role in affective disorders. Abnormalities of thyroid function have been found in adult schizophrenia, anorexia nervosa, and other adult psychiatric disorders [Kolakowska and Swigar, 1977; Cohen and Swigar, 1979]. Disturbances in thyroid hormone regulation have been hypothesized in childhood autism and attention-deficit hyperactivity disorder (ADHD). In a study of 277 ADHD children, there was a higher prevalence of thyroid abnormalities in the ADHD group (5.4%) as compared to the normal controls (<1%) [Weiss et al., 1993]. In another study of 18 families with a history of generalized resistance to thyroid hormone (RTH), 50% of adult subjects with RTH and only 7% of unaffected subjects had met the criteria for ADHD as children ($P < 0.001$). Seventy percent of children subjects with RTH and 20% of unaffected subjects met the criteria for the disorder [Hauser et al., 1993], suggesting that ADHD is strongly associated with generalized RTH. However, further work did not support the association of ADHD and RTH and suggested that RTH is associated with lower IQ scores [Weiss et al., 1994]. Patients with thyroid disease frequently exhibit prominent depressive symptom [Silverstone and Romans-Clarkson, 1989], and thyroid hormone has been used in treatment of depression, bipolar and other psychiatric diseases [Stein and Avni, 1988].

These clinical features suggest that genetic variants in the ER or TR gene may predispose to psychiatric diseases. To investigate this possibility, we analyzed the ERα gene and TRα gene in 113 patients with schizophrenia and performed pilot studies with five other psychiatric diseases.

MATERIALS AND METHODS

Patient Samples

All schizophrenic patients met criteria for the disease as defined by the Diagnostic and Statistical Manual, Third Edition, Revised (DSM-III-R), as described previously [Sobell et al., 1993]. The majority of patients were ascertained through state mental institutions in Minnesota, Washington, and Oregon. Three schizophrenic patients from the Costa Rican population isolate [DeLisi et al., 2000] and three schizophrenic patients from a Finnish population isolate (by L.P.) were also examined. Caucasian females who had experienced at least one episode of puerperal psychosis were recruited through the Division of Neuroscience at the University of Birmingham in the U.K. [Robertson et al., 2000]. Patients with bipolar disorder were ascertained from the U.K. [Jones et al., 2000] or a population isolate in Finland (three patients by L.P.). Patients with alcoholism of Finnish ethnicity were ascertained through collaborative efforts involving the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the University of Helsinki, Finland (by D.G.). Southwestern Native American patients with alcohol dependence were acquired through the NIAAA (by D.G.) [Feng et al., 1998] and patients with autistic disorder or ADHD were ascertained from the University of Chicago [Cook et al., 1995, 1998].

PCR Amplification and DOVAM-S

DOVAM-S is a variant of single-strand conformation polymorphism (SSCP), in which multiple exons are scanned in a single lane under five generic nondenaturing electrophoresis conditions [Liu et al., 1999]. In brief, the exons and associated splice junctions were amplified and pooled by the PE Biosystems catalyst robotic device. The samples were denatured and electrophoresed under five nondenaturing conditions in which gel matrix, buffer, temperature, and additive were varied. PCR primers for the TR gene are listed in Table I and the TR reference gene sequences were from Laudet et al. [1991] (Genbank accessions number: X55004, X55005, and X55066-X55074). PCR primers for the ER gene are as published [Iwase et al., 1996], with minor modifications. The ER gene sequence was taken from Green et al. [1986]. PCR products with mobility shifts were sequenced with the ABI model 377 (Perkin-Elmer Model 377, Norwalk, CT) and nucleotide alterations were analyzed with Sequencher software (Gene Codes, Ann Arbor, MI). Mutations were confirmed by reamplifying from genomic DNA and sequencing in the opposite direction.

Evolutionary Conservation

A phylogenetic tree was constructed for the eight available ER protein sequences in a manner described previously [Feng et al., 2000]. In brief, the roots of the

TABLE I. PCR Primers for TRα gene*

Segment no.	Name	Sequence (5′→3′)
T1	TR-E2 (315)-18D	AGTCTCTTGGCGTGCTGG
	TR-E2 (455)-18U	TGCTGCTTAGGAGTTGGC
T2	TR-E3 (88)-18D	GACTGCTCTGTGATTCTG
	TR-E3 (248)-18U	GCTGGGTTTGGTGGGGTT
T3	TR-E4 (204)-20D	GGAGAGGGGTCAGAAACAAA
	TR-E4 (447)-20U	TTGGGCAAATTGCTTCATCT
T4	TR-E5 (220)-18D	GTCATGATCACAGCCTGC
	TR-E5 (438)-18U	ACCTGGCTCTATTCCCTC
T5	TR-E6 (986)-18D	GAGGGTGCCATGCGTTAG
	TR-E6 (1272)-18U	CACCTGGCTACTGCTCTC
T6	TR-E7 (39)-17D	CCTTGGAGCTCCCCCTGGTG
	TR-E7 (304)-18U	CATCACATCTCTCCCCACTT
T7	TR-E8 (615)-18D	GGGAGGGGTATGCTGAGT
	TR-E8 (945)-18U	CTGAGCCCTCCCGACTAA
T8	TR-E9 (1)-17D	CCCTCACGCCCCTCTTC
	TR-E9 (308)-17U	CAGCTCCGCACACCCTC
T9	TR-E10 (212)-20D	GATTCTGGTTTGCTTTTCCT
	TR-E10 (413)-18U	AGACTTCCCGCTTCACCA
T10	TR-E10 (359)-17D	TTCAGGGTCCGCAGGTC
	TR-E10 (635)-17U	CTTCCCCATCGGCCTTC

*This nomenclature [Sarkar and Sommer, 1989] defines an oligonucleotide specific for the TR gene. E specifies an exon; 315 is the nucleotide number in the reference sequence; the length of the primer is 18 nucleotides; and the orientation is in the downstream direction (D) or the upstream direction (U).

branches were 65 megayears for different orders of mammals, 65 megayears for different orders of birds, 225 megayears for the bifurcation of mammals and birds, and 350 megayears for the bifurcation of amphibians and mammals. Mouse and rat diverged about 20 megayears ago [McLaughlin and Dayhoff, 1972; Colbert, 1980]. The following amino acid sequences were aligned in ERα using the Wisconsin Package (Genetics Computer Group, Madison, WI): human, pig, mouse, rat, chick, Zebra finch, *Xenopus laevis*, rainbow trout, and salmon.

RESULT

DOVAM-S, a form of multiconditional SSCP with a generic set of conditions, has detected all of 250 mutations and polymorphisms in three blinded analyses of the factor VIII, factor IX, and ATM genes [Liu et al., 1999; Buzin et al., 2000]. In this study, the complete coding sequence and splice junctions of ERα and TRα genes were analyzed in 240 DNA samples, including 113 patients with schizophrenia, 28 with BPI, 24 with puerperal psychosis, 5 with autism, 30 with ADHD, 25 with alcoholism, and 15 first-degree relatives of patients with autism or ADHD. A total of 1.18 megabases of the ERα gene and 1.16 megabases of the TRα gene were scanned.

In 480 alleles, only four silent variant alleles of unlikely functional significance were found in the TRα gene: C351T (A117A) in exon 5, C-to-T at −4 of intron 6, C720T (S240S) in exon 7, and C738T (D246D) in exon 8. Each variant was found in a different schizophrenic patient (Table II).

Eight silent mutations or polymorphisms and four missense mutations were identified in the ERα gene (Fig. 1). Three of the four missense mutations are novel; each occurred in one patient. Five of the eight silent mutations are common polymorphisms previously reported by other research groups, while three are rare sequence changes found in one patient each (Table III). When data from both genes are combined, the total of 11 sequence variants were found once in 480 scanned alleles and five sequence variants were found commonly (Table IV). The allele frequencies of common polymorphisms are similar to that previously published in a study of 188 women with primary invasive breast cancer treated at Vanderbilt University Medical Center [Roodi et al., 1995].

DISCUSSION

This analysis illustrates the dramatic difference in variation within genes. Analysis of 240 subjects in ethnically and geographically diverse populations (including the core western Europeans, the Finnish, African Americans, and Pima Indians), revealed only four (silent) variant alleles in TRα gene, while four missense changes and eight polymorphisms, five of them common, were found in the ERα gene. In the present study, no variants affecting protein structure or expression (VAPSEs) were identified when 1.16

TABLE II. TRα Gene Sequence Variants in 480 Alleles

No.	NT change	Amino acid change	Exon	Number of alleles
1	C351T	A117A	5	1
2[a]	IVS6-4 C→T		Intron 6	1
3	C720T	S240S	7	1
4	C738T	D246D	8	1

[a] Intron 6 T Exon 7
CCGTCTTTCTCTCTAG/CCCGATGACA.

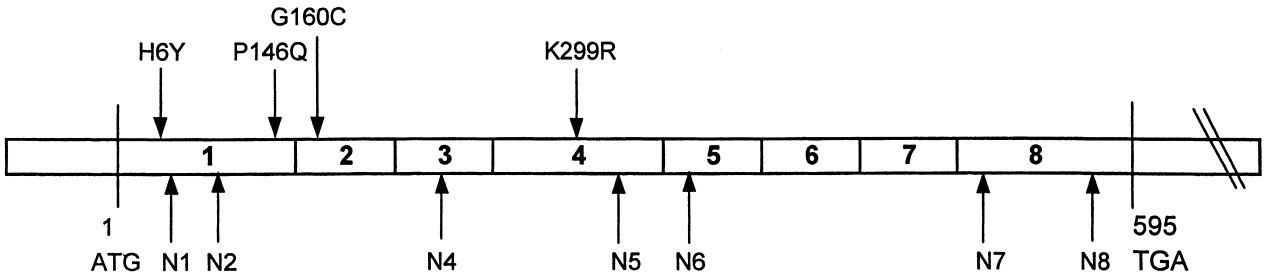

Fig. 1. ERα gene sequence variants. Diagram box shows eight exons of ERα cDNA. VAPSEs are shown above the box labeled with amino acid change. Non-VAPSEs are listed below the box with N-number (see Table III). N3 is not shown.

megabases of the TRα gene were analyzed, suggesting that there is no variation in the coding regions or splice junctions that could be a significant substrate for involvement in the pathological process of psychiatric diseases. However, thyroid hormones may still play a role through interactions with unscanned regulatory regions of TRα gene or interactions with other genes such as TRβ [Shuto et al., 1992].

Of the four VAPSEs in the ERα gene, G160C, identified in one schizophrenic patient, was reported by another research group in two breast cancer patients and one ovarian cancer patient [Anderson et al., 1997]. This mutation was detected in 3 of 239 cancer patients (1.3%) and 8 of 729 controls (1.1%), suggesting that the substitution was not associated with risk for breast cancer.

H6Y, K299R, and P146Q are novel VAPSEs. H6Y and K299R are conserved through zebra finch (465 megayears of evolutionary divergence), while P146Q is conserved through *Xenopus* (940 megayears of evolutionary divergence; Table V). The extent of evolutionary conservation of the wild-type amino acid is promising and hints that the missense mutations are deleterious. In the factor IX gene, mutations causing hemophilia B are almost certain to be deleterious if they occur at amino acids conserved through more than 2,000,000,000 years of evolutionary divergence [Bottema et al., 1991]. These residues are 30-fold more

TABLE III. ERα Gene Sequence Variants in 480 Alleles

No.[a]	Nucleotide change	Amino acid change	Exon	ID[b]/disease	Reference[c]
VAPSEs					
V1	C 248 T	H 6 Y	1	5080-2/BPI	
V2	C 669 A	P 146 Q	1	PS229/alcoholic	
V3	G 710 T	G 160 C	2	S390/schizophrenic	Anderson et al. [1997]
V4	A 1128 G	K 299 R	4	6088-3/puerperal psychosis	
Non-VAPSEs					
N1	T 262 C	S 10 S	1	Common	Roodi et al. [1995]
N2	G 493 C	A 87 A	1	Common	Roodi et al. [1995]
N3	IVS1-15 del T		Intron 1	F386/alcoholic	
N4	C 961 T	R 243 R	3	Common	Roodi et al. [1995]
N5	C 1207 G	P 325 P	4	Common	Roodi et al. [1995]
N6	C 1363 T	H 377 H	5	5228-2/BPI	Anderson et al. [1997]
N7	C 1840 T	L 536 L	8	5058-4/puerperal psychosis	
N8	G 2014 A[d]	T 594 T	8	Common	Roodi et al. [1995]

[a]V:VAPSEs; N: Non-VAPSEs.
[b]ID: patients' ID.
[c]The articles reported the mutations in the ERα gene.
[d]Published sequence of ER cDNA lists ACA as wild-type while ACG found in the majority of samples.

TABLE IV. Allele Frequency of ERα Gene Common Polymorphisms

	T 262 C	G 493 C	C 961 T	C 1207 G	G 2014 A[b]
West European	0.52 (176/338)	0.10 (33/338)	0.02 (7/338)	0.28 (93/338)	0.16 (27/170)
Finnish	0.47 (17/36)	0.06 (2/36)	0 (0/36)	0.19 (7/36)	n/d
African American	0.39 (15/38)	0.03 (1/38)	0 (0/38)	0.18 (7/38)	0.29 (8/28)
American Indian	0.21 (6/28)	0 (0/28)	0 (0/28)	0.36 (10/28)	n/d
Others	0.40 (4/10)	0 (0/10)	0 (0/10)	0.50 (5/10)	n/d
Total[a]	0.48 (218/450)	0.08 (36/450)	0.015 (7/450)	0.27 (122/450)	0.18 (35/198)

[a]Excludes 30 alleles of first-degree relatives of patients with autism or ADHD.
[b]Allele frequency in schizophrenia patients only. n/d: not determined.

TABLE V. Conservation of ERα Gene VAPSEs

No.	Amino acid change	Human	Pig	Mouse	Rat	Chick	Zebra finch	Xenopus	Rainbow trout	Salmon
1	H 6 Y	H	H	H	H	H	H	P	n/a[a]	n/a
2	P 146 Q	P	P	P	P	P	P	P	V	V
3	G 160 C	G	G	N	N	S	S	S	I	I
4	K 299 R	K	K	K	K	K	K	—[b]	—[b]	S

[a]Amino acid not available.
[b]Gap.

likely to be the site of deleterious mutations than amino acids not conserved in mammals.

A preliminary association study [Jones et al., 2000] failed to find evidence for linkage disequilibrium between alleles at two known common nonfunctional polymorphisms in ERα gene and susceptibility to bipolar disorder (n = 219 cases) or puerperal psychosis (n = 26 cases). However, it will be important to extend the findings from the current study by analyzing the VAPSEs in a large sample of subjects and families with both bipolar disorder and puerperal psychosis in order to assess whether there is an association with susceptibility to these disorders.

The ERα gene polymorphisms are located in the region encoding the N-terminal portion of the protein, which has been associated with pathological conditions, including breast cancer, hypertension, spontaneous abortion, and coronary heart disease [Lehrer et al., 1990, 1993; Zuppan et al., 1991]. It has been estimated that somatic missense mutations in the ERα gene occur in about 1% of primary breast cancers [Roodi et al., 1995]. However, the only known germline mutation in the human ERα associated with disease is a point mutation C-to-T at codon 157 of both alleles, resulting in a stop codon, identified in a young adult male with osteoporosis, unfused epiphysis, continued linear growth in adulthood, and estrogen resistance [Smith et al., 1994]. Further analyses are necessary to determine the clinical significance of the four missense mutations identified in this study.

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